

Retapamulin for Reducing MRSA Nasal Carriage
Study Protocol
January 27, 2012
ClinicalTrials.gov ID: NCT01461668

I. BACKGROUND

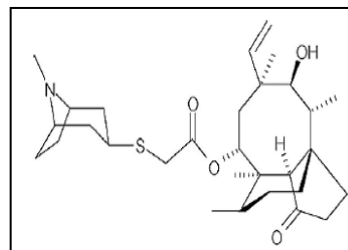
Methicillin-Resistant *Staphylococcus aureus* (MRSA or also known as “mer-sa”) is bacteria (germ) that can be found living on the body, especially in the nose. MRSA infections are common among people who have weak immune systems and are in hospitals, nursing homes, and other health care centers. Infections can appear around surgical wounds or invasive devices, like catheters or implanted feeding tubes. Rates of infection in hospitals, especially intensive care units, are rising throughout the world. Though most MRSA infections are not serious, some can be life-threatening. Many public health experts are alarmed by the spread of antibiotic-resistant bacterial strains like MRSA, which are also known as “super bugs.”

Currently, prevention for MRSA is restricted to education for the public and patients who harbor MRSA. Currently, some physicians will attempt to rid MRSA from the body to prevent later infection using special soaps and medicines. Use of these strategies is variable since no definitive guidance exists for their use. Currently, one of the medications to eradicate MRSA from its most common body reservoir, the nose, is a drug known as mupirocin. Mupirocin is an ointment approved for MRSA removal. However, in recent years, resistance to mupirocin is rising among MRSA strains. A second drug, retapamulin has been shown in the laboratory to be highly active against all MRSA strains, even mupirocin resistant ones. While retapamulin is FDA approved for use in open wounds and skin infections, it is not currently approved for use in the nose. The purpose of this study is to evaluate whether retapamulin (an FDA approved topical ointment for treatment of staphylococcus) which is commonly used to treat MRSA wound infections, may work in clearing MRSA from the noses of people who have MRSA types that are resistant to mupirocin. The route of administration that will be investigated is to apply the ointment via the nasal passage twice daily for up to 5 days. The effects of retapamulin will be compared to placebo (inactive similar ointment) in a randomized placebo controlled double-blinded trial.

II. INVESTIGATIONAL PRODUCT

Altabax (retapamulin) has been FDA approved since April 2007 for use in the topical treatment of impetigo due to susceptible strains of *Staphylococcus aureus* or *Streptococcus pyogenes*, the two most common types of bacteria in this kind of infection.

Altabax (retapamulin) is a semisynthetic pleuromutilin antibiotic. The chemical name of retapamulin is acetic acid, [[[3-exo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]thio]-, (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-6-ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9propano-3a*H*-cyclopentacycloocten-8-yl ester. Retapamulin, a white to pale-yellow crystalline solid, has a molecular formula of $C_{30}H_{47}NO_4S$, and a molecular weight of 517.78.



Altabax (retapamulin) has not been withdrawn from investigation or marketing in the United States or any other country for any reason related to safety or effectiveness.

III. PURPOSE & OBJECTIVES

The purpose of this study is to evaluate altabax (retapamulin) as an investigational agent for decolonizing MRSA carriers with high-level resistance to mupirocin. Mupirocin resistance is increasingly common and there is no approved substitute topical agent for decolonization of the MRSA nasal reservoir.

Objectives

1. Evaluate the proportion of patients treated with retapamulin vs placebo who clear nasal carriage with a mupirocin-resistant strain of MRSA
2. Evaluate the time to MRSA clearance among patients treated with retapamulin vs placebo for nasal carriage with a mupirocin-resistant strain of MRSA (one treatment course or two)
3. Evaluate side effects reported with nasal administration of retapamulin compared to placebo

IV. STUDY DESIGN

This is a randomized placebo-controlled double-blind study of nasal decolonization with retapamulin vs. placebo for the eradication of MRSA nasal carriage among adult carriers with mupirocin resistant strains. Randomization of eligible patients will be stratified by participants with low-level (MIC 8-256) and high-level mupirocin resistant (MIC >256) strains.

Eligible subjects will be randomized to 1% retapamulin or placebo ointment intra-nasally twice a day for 5 days (D1-5) with follow up bilateral nares swab one week following completion of therapy (~D12) to assess clearance. If follow up swabs are positive for MRSA, subjects will be given a second course of the same agent (retapamulin or placebo) to begin one week following swab collection (~D19-23) so that up to two decolonization attempts will be made. A final set of bilateral nares swabs will be obtained from all subjects six weeks from the completion of initial treatment (~D47).

Overview for Study Participants

Consent Date	Swab nares, complete survey
Day 0	Swab confirms mupirocin-resistant MRSA, provide 5-day protocol (retapamulin vs placebo)
Day 1	Initiate 5-day protocol (retapamulin vs placebo)
Day 12	Follow Up Visit 1, complete survey, swab nares
	If nares from day 12 still shows MRSA, repeat 5-day protocol
Day 47	Follow Up Visit 2, complete survey, swab nares

Consenting subjects will be given retapamulin or a placebo. Additionally, all subjects will be given an education material to follow standard-of-care for patients harboring MRSA. At the time of recruitment, all subjects will complete a detailed survey administered by trained members of research team. This survey will include questions related to comorbidities and presence of wounds or central lines. Subject follow up will include repeat bilateral nares swabs and follow up surveys related to compliance with the assigned regimen and will occur either during a home visit (or facility visit if the patient is admitted to a hospital or nursing home at the time of the required visit) or at the University of California Irvine (UCI) Institute for Clinical and Translational Science (ICTS), a Clinical and Translational Science Award (CTSA) site.

V. OUTCOMES

Primary outcome will be successful nares decolonization at the end of the follow up period (D47). The members of the research team will also detail the sequence of clearance or re-colonization based upon the two follow up nares swabs with and without re-treatment by assigned protocol. We will define any adverse events, which are expected to be related to local irritation in a small percent of subjects (1.4% reported site irritation when applied to lesions, as per package insert). As a potential corollary, use of the nasal product mupirocin, which is FDA approved for intranasal use for MRSA clearance resulted in <1% of patients in clinical trials withdrawing due to adverse events. With mupirocin, the most frequently reported adverse events were as follows: rhinitis (1.0%), taste perversion (0.8%), and pharyngitis (0.5%).

VI. DURATION OF INDIVIDUAL SUBJECTS EXPOSURE TO DRUG

Eligible subjects who are randomized to 1% retapamulin intra-nasally will be directed to apply it twice a day for 5 days. For those that fail to clear MRSA by their first follow up visit, a second course directing application of retapamulin twice a day for an additional 5 days will be provided to allow up to two decolonization attempts to be made.

VII. DESCRIPTION OF THE OBSERVATIONS AND MEASUREMENTS TO BE MADE TO FULFILL THE STUDY OBJECTIVES

At the time of recruitment, all subjects will complete a detailed enrollment survey administered by trained research staff. This survey will include enrollment information (demographic, contact), questions related to self care, home hygiene practices, high contact sports or other activities, comorbidities, and presence of wounds or central lines. They will also have a nasal swab performed to confirm the presence of MRSA carriage with a strain resistant to mupirocin. Once swab cultures confirm the presence of MRSA resistant to mupirocin, subjects will be randomized to receive 5-days of either placebo or retapamulin with the first treatment day being Day 1. Subject follow up will include repeat bilateral nares swabs (Day 12 (range 9-15), Day 47 (range 37-57) and follow up surveys related to compliance and experience (side effects/concerns) with the assigned regimen and will occur either during a home visit (or facility

visit if the patient is admitted to a hospital or nursing home at the time of the required visit) or at the University of California Irvine (UCI) Institute for Clinical and Translational Science (ICTS). All study subjects will have subject enrollment and follow-up data maintained in a secure electronic database that only authorized members of the study team will have access to.

VIII. MEASURES TAKEN TO MONITOR THE EFFECTS OF THE DRUG IN HUMAN SUBJECTS AND TO MINIMIZE RISK

This topical agent is already FDA approved for application to the skin. The novel use requested here is application to the nasal mucosa. An FDA IND has been received for its use in this study as a nasal product. Previous studies with retapamulin on abraded skin failed to show sufficient absorption to raise concerns about the drug itself or interaction with systemic agents (see package insert). Thus, in this, there will be no direct testing of the systemic levels of this drug.

To determine if retapamulin is effective in reducing MRSA clearance, serial bilateral nares swabs will be taken to confirm MRSA mupirocin resistance and to assess persistence of MRSA carriage during this study. A toll free number and 24/7 pager that will be answered by the study team will be available to subjects for the reporting of any side effects. In addition, a survey assessing compliance and side effects/concerns with the assigned regimen will be performed during all follow up visits.

IX. RECRUITMENT METHODS

The recruitment process will be initiated by study staff who have experience recruiting patients into clinical trials and are familiar with the protocol and the consenting process. This study to evaluate the safety and efficacy of intra-nasal retapamulin for decolonization of mupirocin-resistant MRSA carriers will be conducted in our California regional trial environment where patients will be recruited through one of the following methods:

1) Subjects previously enrolled in a randomized clinical trial (Clinicaltrials.gov ID: NCT01209234) found to have low-level (MIC 8-256) or high level (MIC >256 mcg/ml) mupirocin-resistant MRSA strains at the end of their follow up period will form one source of recruitment into the retapamulin study. Willing subjects would consent to a current screening MRSA swab at the time of recruitment to confirm the presence of a mupirocin resistant isolate. Patients will be randomized within strata of low level and high level mupirocin-resistant strains.

2) Patients with MRSA isolates processed for mupirocin resistance at the University of California Irvine Medical Center clinical microbiology laboratory will also be eligible for recruitment if harbored MRSA strains show low level or high level resistance. Patients will be similarly randomized based upon strata of low level and high level mupirocin-resistant strains.

To ensure that a subject has the option to speak with a physician at the end of the consent process, a study doctor will be available via pager or phone to answer any questions or concerns a subject might have prior to finalizing consent.

Review and approval of this human protocol will be conducted by the UCI Institutional Review Board (IRB) Human Subjects Review Committee. Subjects must be able to understand and sign an informed consent form. Consent forms must comply with U.S. regulations (U.S. 21 CFR 50) and ICH guidelines to be eligible for this trial. All study materials, including consent forms will be provided in the patient's primary language. In addition, each subject will be given a copy of the consent form, the Experimental Subjects' Bill of Rights, and HIPAA Release form, all of which will be explained to the subject.

X. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. Adult, at least 18 years of age or older
2. MRSA carrier of a mupirocin resistant strain
3. Must be able to provide consent

Exclusion Criteria

1. Known allergy to retapamulin
2. Inability to use an intranasal product (e.g. recent nasal surgery, anatomic defects)
3. Pregnant or breastfeeding

Children (under the age of 18 years old) will be excluded since post-carriage MRSA risks have not been studied among those <18 years old and there is insufficient data to estimate the effect or potential benefit in this age group. This also translates to an inability to calculate power or sample size needs to answer the questions in this trial for children <18.

In addition, there are several reasons to believe that the risk in children <18 will be different from those in adults. First, and most importantly, they have a much lower frequency of risk factors for MRSA disease, including comorbidities, medical devices and procedures. Second, their risk of MRSA carriage has been found to be lower than in adults. Third, children experience a much higher proportion of disease due to community-associated MRSA infection (and strains) versus healthcare associated infections (and strains). These differences suggest that the mechanisms for MRSA acquisition may be different in children compared to adults. Fourth, children also experience much more skin and soft tissue disease and less of other types of infections, again suggesting substantial differences in children and adults that would support a separate trial in this age group. For all these reasons, we will exclude children under the age of 18.

Women who are pregnant or breastfeeding will be excluded from the study. Retapamulin is Pregnancy Category B drug, defined by the FDA as an agent in which animal reproduction studies have failed to show a risk to the fetus. The effects of retapamulin on fertility or a human fetus are not known, however absorption is deemed so minimal that pharmacokinetic studies were not deemed necessary by the FDA. Animal studies have been performed and have not shown concerns; however since animal studies are not always predictive of human response,

retapamulin should only be used on pregnant women if clinically necessary. Despite minimal absorption, as a precautionary measure, we will not be recruiting patients known to be pregnant or breastfeeding into this study. In addition, we will recommend abstinence or contraception for those who wish to participate. However, since the current FDA approved usage of retapamulin on open wounds does not require a pregnancy test nor contraception, we will only recommend, but not require, that all subjects abstain from sexual activity or use birth control while taking study product.

XI. RISKS AND DISCOMFORTS

Subjects are informed of the risks and side effects that are known to possibly occur due to Retapamulin and procedures involved during this study. Subjects are also instructed to contact their study doctor or a member of the study team immediately if they experience any problems during the course of the study. All subjects will be closely monitored throughout the study and may be asked to come into UC Irvine for an unscheduled visit, at the discretion of the lead researcher. In addition, all subject data will be de-identified with a key-code and only the study team and authorized individuals involved with the study will have access to the code. All measures will be taken by the study team to protect the confidentiality of every subject's personal health information.

XII. ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

All adverse events will be tracked until resolved or participation in the study has ended, whichever comes first. All serious adverse events will be tracked until resolved. In accordance with UCI IRB's guidelines, all adverse events and unanticipated problems will be reported per policy. There will be a Data Safety Advisory Committee to oversee the number and composition of adverse events, and assess any need for intervention or discontinuation of study protocols

Study coordinators will be available from 8am-5pm via a toll-free phone number. Should a subject require immediate assistance after hours (5pm – 8am) or on weekends, the Senior Project Coordinator and Supervisor will be available via pager. The Senior Project Coordinator and Supervisor can assist the subject with any questions and concerns and can promptly put them in contact with study investigators as needed. In addition, study staff will query for adverse events or other unanticipated problems via phone calls and during scheduled follow up visits. If adverse events are identified, subjects may be referred for a phone conversation or in person visit with a nurse or physician at ICTS. If an adverse event is serious, the subject is instructed to contact 911 or go to the nearest Emergency Department for immediate care.

XIII. PARTICIPANT COMPENSATION AND REIMBURSEMENT

Subjects will be required to have two follow-up visits at 2 weeks and 6 weeks from randomization. Subjects will be compensated \$25 for the first follow-up visit and \$25 for the

second follow-up visit with cash payment. Total payment for participation in this study is \$50. If subjects cannot attend the follow-up visits, recruiters will drive to their location and perform the follow-up procedures there. If subjects decide to withdraw from the study or are withdrawn by the study team, they will receive compensation for the visits that they have completed.